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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,454	09/14/2000	Masayuki Yanagi	2026-4276US1	9114

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,454	YANAGI ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/1/06.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 58-66 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 58- 63 is/are allowed.

6)☒ Claim(s) 64-66 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/1/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 5/1/06 and a Declaration under 37 CFR 1.132 by Dr. Purcell. Claims 1-57 are canceled. Claims 60 and 61 are amended. Claims 58-66 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Information Disclosure Statement

An IDS filed 5/1/06 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 64-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. **This rejection is maintained for reasons of record in the office action mailed 1/27/06 and restated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

1) **Nature of the invention**: Claim 64 is directed toward a method for inducing an immune response in an animal by administration of a composition comprising either SEQ ID NO:3 or chimeric molecules comprising replacing sequences encoding structural proteins or HCV proteins of SEQ ID NO:3 with HCV sequences from HCV from another strain or genotype which upon expression in transfected cells results in production of virus.

2) Scope of the invention: The composition is provided to an animal that is not infected with HCV (claim 65) or is infected with HCV (claim 66). According to the specification, the nucleic acid composition is to be used as a therapeutic agent. Hence, the methods are practiced on *any* animal either that is susceptible to HCV infection or not to prevent and treat hepatitis C infection by hepatitis C virus (HCV). The scope of the invention thus exacerbates a complex art.

3) Number of working examples and guidance. Applicants have isolated the first full infectious clones of HCV, H77 genotype 1a (SEQ ID NO:1 and 2) and strain HC-J4 (SEQ ID NO:3 and 4), genotype 1b. Previously isolates were non-infectious in cell culture. The instant clones differ from those of the prior art by inclusion of portions of the 3' end determined to be essential for infectivity (see e.g. figure 17A-17G and page 52, line 4-14). As well, applicants

have generated a chimera of clones 1a and 1b (SEQ ID NO:5 and 6). In figure 18, the infectivity of the instant clones and production of anti-HCV antibodies by chimpanzees infected with HCV was demonstrated. Hence, genetically stable clones of HCV were constructed from both clones and are able to induce the production of antibodies. Administration of these clones is then proposed to be useful prophylactic ally in subjects previously infected or not, which uses embrace methods of immunization against HCV to prevent HCV infection as well as methods of treatment (see e.g. page 20-21). Induction of antibodies is also said to be useful in diagnostic purposes (see page 24). Applicants have also provided post-filing art demonstrating the production of anti-HCV antibodies from a genotype 1b (Yanagi et al, 1998).

4) State of the art. HCV is a human pathogen comprising six major genotypes and a number of subtypes and variants. Chronic infection is responsible for cirrhosis and hepatocellular carcinoma and represents the most frequent indication for liver transplantation in developed countries (see e.g. Forns et al, 2002). The development of vectors for vaccination to protect or treat HCV infection is of importunate concern as HCV infection has no viable treatment plan. Despite the pressing nature of a vaccine, there have been no promising or potential developments to date. Protective immunity has not been possible for a variety of reasons such as the genetic heterogeneity of HCV. Even within an individual, HCV circulates as a mixture of closely related but distinct genomes. Immunity appears to be strain and isolate specific. Forns et al teach that chimpanzees with effective immunity against homologous genotype1a were not protected against challenge with genotype 1b (see e.g. page 685, col1, paragraph 2). Furthermore, the virus has an inherent ability to escape immunity (see e.g. page 685, col2, paragraph 1).

At the time of filing for the instant application no known vaccines effective for the treatment of animals infected by HCV or effective in the prophylactic protection against HCV infection. The prior art teaches "Despite great progress in understanding the natural history of the disease, fundamental aspects of the pathogenesis of hepatitis C remain unknown." (Nelson Fausto, American Journal of Pathology, August 1997, Vol. 151, No. 2, page 361, first column).

5) Unpredictability of the art: Applicants claims are drawn to a method of inducing an immune response in infected and non-infected animals. The specification teaches that the goal of induction of the immune response is for prevention and treatment. However, the art has demonstrated that even partial protection has not been attainable and therapeutic vaccines are faced with multiple obstacles such as the ability of the virus to persist in the cell despite the production of antigens (see Rice, 2006, page 3). The most promising approach is believed to involve a spectrum of treatments as no single treatment plan has prove ineffective and the lack of understanding of the virus has hindered effective progress on developing a vaccine and lack of reproducible cell-culture systems and small animal models has created technical limitations (see Forns et al, section 2.2-2.4). Hence, it is highly unpredictable that a method of introducing a DNA construct comprising the nucleic acid constructs of the instant invention would generate a functional vaccine against HCV or a therapeutic treatment of HCV infection.

6) Amount of Experimentation Required: The invention recites a generation of nucleic acid constructs for use in vaccination to induce an immune response. The unpredictability of using the claimed invention in vaccination is accentuated due to the lack of methods or processes disclosed in the instant specification for development of a successful vaccine that exacerbates a highly unpredictable art.

In view of unpredictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 112. first paragraph on page 4 of the amendment filed 5/1/06 and in the Declaration under 37 CFR 1.132 by Dr. Purcell. Dr. Purcell argues that administration of the recited clones is to be useful prophylactically and therapeutically embracing methods of immunization against HCV to prevent and treat HCV infection. It is applicants assertion that the claims "which require induction of an immune response, are met by the demonstration of the production of antibodies". Applicants counter the assertion that the possibility that immunity against HCV is strain or isolate specific and that genetic heterogeneity of the virus contributes to escape from preexisting immunity by arguing that this does not antagonize vaccination against HCV. Pointing to data from Forns et al, applicants argue that neutralizing antibodies were found in infected HCV and as such suggest that a vaccine is a reasonable goal and a such is met by the demonstration of the production of antibodies and not complete neutralization or full immunity but will contribute to neutralization and immunity. Secondly, applicants argue that analysis of the pathogenesis of HCV is possible

given the development of a cell culture system and small animal model. Finally, applicants argue that the utility of claims 64-66 is unquestioned.

Applicants' arguments filed 5/1/06 have been fully considered but they are not persuasive. As to the utility of the instant claims, the instant claims have not been based on a lack of utility of the instant claims but rather that a person of skill in the art would be unable to practice the invention as claimed given the highly unpredictable nature of the art of inducing an immune response in an animal not infected or infected with hepatitis C virus. While applicants argue that the claims embrace demonstration of the production of antibodies, the production of antibodies is meant for therapeutic and prophylactic responses for HCV infection. On page 6, ¶ 2 and 3, the specification states "The invention therefore also relates to vaccines for use in immunizing mammals especially humans against hepatitis C" and "The present invention therefore relates to methods for preventing hepatitis C in a mammal". The claims as recited are directed to vaccination and treatment against HCV infection, antibody production is directed towards these ends. Based upon this disclosed use and the unpredictability of the art, the claims would require undue experimentation.

Conclusion

Claims 58-63 are allowed.

Claims 64-66 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300 for regular communications and (571) 273-8300 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1633

January 21, 2006

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER